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TOWNSEND and TOWNSEND and CREW LLP
By:

PATENT
Attorney Docket No. 02307O-115611US
Client Ref. No. 2000-094-3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Deanna L. KROETZ et al.

Application No.: 10/694,641

Filed: October 27, 2003

For: INHIBITORS OF EPOXIDE HYDROLASES FOR THE TREATMENT OF HYPERTENSION

Confirmation No. 4011

Examiner: Brian Yong Kwon

Technology Center/Art Unit: 1614

APPELLANTS' BRIEF UNDER 37 CFR §41.37

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal submitted on November 26, 2008 for the above-referenced application, Appellants submit this Brief on Appeal.

TABLE OF CONTENTS

1. REAL PARTY IN INTEREST 3

2. RELATED APPEALS AND INTERFERENCES 4

3. STATUS OF CLAIMS 5

4. STATUS OF AMENDMENTS 6

5. SUMMARY OF CLAIMED SUBJECT MATTER 7

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL 9

7. ARGUMENT 10

8. CONCLUSION 20

9. CLAIMS APPENDIX 21

10. EVIDENCE APPENDIX 22

11. RELATED PROCEEDINGS APPENDIX 23

1. REAL PARTY IN INTEREST

The real parties in interest in this appeal are the following:

(i) The Regents of the University of California, Oakland, California, which is the assignee; and

(ii) Arête Therapeutics, which is the exclusive licensee.

2. RELATED APPEALS AND INTERFERENCES

NONE.

3. STATUS OF CLAIMS

A. TOTAL NUMBER OF CLAIMS IN APPLICATION

There are two (2) claims pending in the application, namely, claims 46 and 48.

B. STATUS OF ALL THE CLAIMS IN APPLICATION

Claims canceled: 1-45, 47 and 49-53

Claims withdrawn from consideration but not canceled: NONE

Claims pending: 46 and 48

Claims allowed: NONE

Claims rejected: 46 and 48

Claims objected to: NONE

C. CLAIMS ON APPEAL

The claims on appeal are: 46 and 48

4. STATUS OF AMENDMENTS

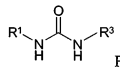
Appellants submitted an amendment on November 26, 2008 in response to the Final Rejection mailed on September 17, 2008, canceling claims 47 and 49-53 and submitting a Notice of Appeal. This amendment has not been acknowledged by the Examiner.

Claims 46 and 48 on appeal herein are as amended in the Response to Office Action submitted on October 29, 2007. This amendment was entered and acknowledged by the Examiner in the Non-Final Office Action mailed on February 7, 2008.

5. SUMMARY OF CLAIMED SUBJECT MATTER

A. CLAIM 46 – INDEPENDENT

The subject matter of claim 46 is directed to a method of reducing blood pressure in a patient by administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase (sEH), wherein said inhibitor is a compound or a pharmaceutically acceptable salt thereof having a structure of:



Formula I

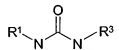
wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

The method of claim 46 requires the administration of a compound that has the functional requirement of inhibiting sEH and the structural requirement of having the structure of Formula I, depicted above, wherein both of the R substituents are independently C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

Support is found, for example in the Specification, *e.g.*, at the abstract, in Table 1 on pages 3-13 and in paragraphs [0007-0008] and [0016]. The operability of the claimed method is demonstrated in the Example provided on pages 28-34 of the Specification, and in Figures 4-5 and in paragraphs [0014-0015].

B. CLAIM 48 – INDEPENDENT

The subject matter of claim 48 is directed to a method of reducing hypertension in a patient, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase, wherein said inhibitor or a pharmaceutically acceptable salt thereof is a compound having a structure of:



Formula I

wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

The method of claim 48 requires the administration of a compound that has the functional requirement of inhibiting sEH and the structural requirement of having the structure of Formula I, depicted above, wherein both of the R substituents are independently C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

Support is found, for example in the Specification, *e.g.*, at the abstract, in Table 1 on pages 3-13 and in paragraphs [0007-0008] and [0016]. The operability of the claimed method is demonstrated in the Example provided on pages 28-34 of the Specification, and in Figures 4-5 and in paragraphs [0014-0015].

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 46 and 48 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 5,962,455 (hereinafter "Blum").

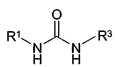
7. ARGUMENT

A. GROUND OF REJECTION

Claims 46 and 48 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 5,962,455 (hereinafter "Blum")[1].

Independent Claim 46 reads as follows:

46. A method of reducing blood pressure in a patient, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase, wherein said inhibitor is a compound or a pharmaceutically acceptable salt thereof having a structure of:

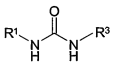


wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

[1] U.S. Patent No. 5,962,455 is attached as Evidence Appendix IA.

Independent Claim 48 reads as follows:

48. A method of reducing hypertension in a patient, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase, wherein said inhibitor or a pharmaceutically acceptable salt thereof is a compound having a structure of:



wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

B. TEACHINGS OF APPELLANTS CLAIMED EMBODIMENTS

Through embodiments of their invention, Appellants provide methods for reducing hypertension and blood pressure in a patient by administration of an inhibitor of the enzyme soluble epoxide hydrolase ("sEH"). Appellants were the first to identify the relationship between the enzymatic activity of sEH and increased hypertension and/or blood pressure.

As explained in the background section of the Specification, arachidonic acid is metabolized in mammals by cytochrome P450 (CYP) epoxygenases to yield epoxyeicosatrienoic acids (EETs). EETs are further hydrolyzed by the enzyme soluble epoxide hydrolase (sEH) to the corresponding dihydroxyeicosatrienoic acids (DHETs). EETs have vasodilatory properties and modulation of EETs is associated with corresponding changes in blood pressure. Therefore, increasing levels of EETs reduces blood pressure and hypertension. Levels of EETs can be increased by increasing metabolism of arachidonic acid by cytochrome P450 (CYP) epoxygenases and/or by decreasing hydrolysis by sEH. Prior to the present invention, modulating EET levels by regulation of their hydrolysis to the less active diols (*i.e.*, DHETs) was not considered in light of concerns that EETs are involved in many physiological processes. *See*, the Specification at page 2, lines 22-25.

The present invention is based on the demonstrated observation that inhibition of EET hydrolysis *in vivo* by inhibition of sEH enzyme activity is associated with elevated EET levels and a reduction in blood pressure. The "downstream" approach of inhibition of EET hydrolysis by inhibition of sEH provides an alternative method to decrease blood pressure and counteract hypertension.

A simplified pathway depicting the synthesis of EETs from arachidonic acid the hydrolysis of EETs by sEH to DHETs is depicted below.

arachidonic acid (AA)

cytochrome P450 (CYP) → ↓
increase metabolism of AA

epoxyeicosatrienoic acids (EETs)

soluble epoxide hydrolase (sEH) → ↓
decrease hydrolysis of EETs

dihydroxyeicosatrienoic acids (DHETs)

C. REJECTION OF CLAIMS 46 AND 48

On page 3 of the Final Office Action mailed on September 17, 2008, the Examiner takes the position that

> "Blum teaches use of compounds (e.g., RN 202472-67-1, RN 202472-68-2, RN 202472-69-3, RN 202472-70-6, etc...) or their salt, which reads on the instantly claimed compounds of the formula 1, for the treatment of the claimed cardiovascular disease such as hypertension or essential hypertension as well as congestive heart failure, wherein said compound is administered in dosage amounts of from about 0.1 mg to about 140 mg per kilograms of body weight per day and in various dosage forms including oral dosage form (abstract; column 1, line 39; column 1, line 45 thru column 3, line 15; column 7, line 51; column 8, line 52 thru column 10, line 62)."

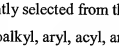
On pages 6-7 of the Final Office Action mailed on September 17, 2008, the Examiner stated the following:

> "Applicant's argument in the response takes the position that the substituted benzylamine derivative compounds disclosed by Blum are unlikely to inhibit sEH activity rather than necessarily inhibit sEH because of the structural unrelatedness of human NPY1R and human sEH proteins and bulkiness of at least one of the substituents (i.e., the substituent that has more than 20 carbons). Applicant alleges that Exhibits submitted on June 02, 2008 and Dr. Bruce Hammock's Declaration submitted on June 13, 2006 and February 23, 2007 confirm that the substituted benzylamine derivative compounds of Blum are unlikely to inhibit the enzymatic activity of sEH.
>
> This argument is not found persuasive. With respect to Dr. Hammock's Declaration, the examiner likes to point out that there is no conclusive statement or data showing that the compounds of Blum do not show any inhibitory activity of sEH. Rather, Dr. Hammock stated that the referenced compounds (e.g.,

compound RN 202472-69-3 and RN 202472-70-6) could be "mediocre activity" (see page 7 of Declaration filed 06/13/06). In other words, it is clear from Dr. Hammock's statement that the compounds of Blum possess some degree (little to moderate) of sEH inhibitor activity. Since the instant claims 46 and 48 do not specifically recite how much of sEH enzymatic activity is required to practice the claimed invention, the prior art directing the administration of the same compound in overlapping dosage amounts (see "0.001 μM/kg to about 100mg/kg body weight" in para. [0060] of the instant specification) inherently possessing therapeutic effect for the same ultimate purpose (e.g., the treatment of hypertension) as disclosed by the applicant clearly anticipates the claimed invention even absent explicit recitation of underlying mechanism."

D. THE METHODS OF CLAIMS 46 AND 48 ARE NOVEL OVER BLUM

As the Office is aware, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). The present methods require administering a therapeutically effective amount of a compound (i) that has the structure



wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic; and (ii) functionally is an inhibitor of soluble epoxide hydrolase ("sEH").

Blum does not expressly describe a method of reducing hypertension or blood pressure by inhibiting sEH in any instance, including by administration of an sEH inhibitor as recited in claims 46 and 48. Blum also does not inherently describe the claimed methods.

The Burden for Inherent Anticipation Has Not Been Met[2]

The Office concedes that Blum is silent about the functional characteristic of the substituted benzylamine derivative compounds to inhibit sEH, but alleges that such property or characteristic is inherent in the compounds disclosed by Blum. *See, e.g.*, pages 6-7 of the Office Action mailed on September 17, 2008, page 10 of the Office Action mailed on December 29, 2005 and page 11 of the Office Action mailed on August 23, 2006.

The Office has not met its burden for alleging inherent anticipation of the claimed methods based on the disclosure of Blum. According to the M.P.E.P., "[t]he fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic (emphasis in original; *citing In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) and *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)). *See*, M.P.E.P. § 2112 (IV). *See also*, *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1986) ("[T]he examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency.).

The M.P.E.P. goes on to quote *In re Robertson* as stating "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is ***necessarily present*** in the thing described in the reference, ***and that it would be so recognized by persons of ordinary skill***. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient' " (emphasis added; *quoting In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). *Id.* The M.P.E.P. reiterates the standard for establishing a rejection of inherent anticipation by quoting *Ex parte Levy* as stating "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the

[2] Arguments made on page 11 of the response submitted on June 2, 2008 regarding the size of the substituents on the NPY1R inhibitor compounds of Blum are no longer maintained.

teachings of the applied prior art." (emphasis in original; *quoting Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990).

Here, Appellants respectfully maintain that the Examiner has not provided evidence or scientific reasoning to show that any compound of Blum inhibits sEH at all, much less sufficiently to reduce hypertension or blood pressure. Instead, Blum discloses that their substituted benzylamine derivative compounds selectively bind to mammalian neuropeptide Y1 receptors (NPY1R) and inhibit the activity of neuropeptide Y. A BLAST alignment of the amino acid sequences of human NPY1R (GenBank accession number AAS55647) and human sEH (GenBank accession number AAG14968) shows that they are structurally disparate proteins, sharing no significant sequence homology.[3] Moreover, human NPY1R and human sEH do not share commonly conserved protein structural domains. Whereas human sEH has the conserved domains alpha/beta hydrolase ("Abhydrolase_1," pfam00561) and a hydrolase superfamily domain COG1011, human NPY1R has the conserved domain for 7 transmembrane receptors (rhodopsin family) ("7tm_1," pfam00001).[4] Not surprisingly, BLAST searches inputting a human NPY1R amino acid sequence do not retrieve any human sEH sequences.[5] Likewise, BLAST searches inputting a human sEH amino acid sequence do not retrieve any human NPY1R sequences.[6] In view of the structural unrelatedness of human NPY1R and human sEH proteins, those of skill would expect that compounds that bind to NPY1R and interfere with the function of neuropeptide Y are unlikely to inhibit the enzymatic activity of sEH. Likewise, those of skill would expect that compounds that inhibit the enzymatic activity of sEH are unlikely to bind to NPY1R, regardless of a common urea or thiourea pharmacophore.

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[3] Copies of GenBank entries AAS55647 and the BLASTp pairwise alignment to soluble epoxide hydrolase are attached as Evidence Appendix IIC.

[4] Copies of BLAST searches inputting the amino acid sequences of human NPY1R, and the identified conserved domains, are provided as Evidence Appendix IID. Copies of BLAST searches inputting the amino acid sequences of human sEH, and the identified conserved domains, are provided as Evidence Appendix IIE.

[5] See, Evidence Appendix IID.

[6] See, Evidence Appendix IIE.

This is confirmed by the Rule 132 Declarations submitted by Dr. Bruce Hammock on June 13, 2006[7] and February 23, 2007[8]. With respect to the specific substituted benzylamine derivative compounds disclosed by Blum, Dr. Hammock attests that they are unlikely to effectively inhibit an sEH because at least one of the substituents (*i.e.*, the substituent that has more than 20 carbons) is too bulky to inhibit the catalytic site of the sEH enzyme. *See*, paragraphs 12-13 of the Rule 132 Declaration of Dr. Hammock submitted on June 13, 2006. Dr. Hammock recognizes and attests that the substituted benzylamine derivative compounds of Blum are designed to target a different molecule (*i.e.*, NPY1R), and that they would be inactive as inhibitors of sEH. *Id.* at paragraph 13.

Therefore, those of skill would recognize that the substituted benzylamine derivative compounds disclosed by Blum are unlikely to inhibit sEH activity rather than ***necessarily*** inhibit sEH, the standard required for inherent anticipation. Blum discloses that the substituted benzylamine derivative compounds selectively bind to NPY1R, a protein that is structurally disparate from sEH. Those of skill will readily recognize the structural and functional unrelatedness of NPY1R and sEH. Dr. Hammock's Declaration confirms that the substituted benzylamine derivative compounds disclosed by Blum are unlikely to inhibit sEH activity rather than ***necessarily*** inhibit sEH.

The Office has attempted to shift the burden of proving the absence of inherent anticipation onto Appellants without first showing a sound basis for believing that the compounds of the present methods and the compounds used by Blum are the same, both functionally and structurally. *See*, M.P.E.P. § 2112.01. The Office has not met this burden to establish inherent anticipation. Regardless, Appellants have rebutted any alleged *prima facie* case of inherent anticipation by providing evidence showing that the compounds disclosed in Blum do not ***necessarily*** possess the characteristics of the compounds in the claimed methods. Even possessing a common urea or thiourea pharmacophore, the substituted benzylamine derivative compounds disclosed by Blum, which have the function of binding to NPY1R, are structurally and functionally distinct from the sEH inhibitors used in the present methods. The

[7] Attached as Evidence Appendix IIA.

BLAST alignments showing the unrelated structure of NPY1R and sEH, the Declarations of Dr. Hammock, and the disclosure of Blum itself, all support Appellants' assertion that the substituted benzylamine derivative compounds disclosed by Blum do not ***necessarily*** possess the functional characteristic of inhibiting sEH, a required attribute of the compounds in the claimed methods. Accordingly, the standard for asserting inherent anticipation has not been met.

Blum does not Disclose or Suggest Any Nexus between sEH Inhibitors and Reducing Blood Pressure or Hypertension

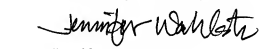
The present invention is directed to ***methods*** of reducing hypertension or blood pressure by inhibiting sEH. Blum does not disclose or suggest anything regarding inhibiting sEH, much less identify a nexus between the inhibition of sEH and the therapeutic benefit of reduced blood pressure and/or hypertension. Instead, Blum discloses methods of inhibiting the function of neuropeptide Y by employing compounds designed to selectively binding to NPY1R.

[8] Attached as Evidence Appendix IIB.

8. CONCLUSION

For all of the foregoing reasons, Appellants respectfully submit that the methods of claims 46 and 48 are not anticipated by Blum. It is respectfully requested that the Board reverse the Examiner's final rejection of claims 46 and 48.

Respectfully submitted,



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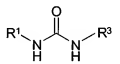
9. CLAIMS APPENDIX

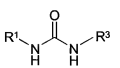
The text of the claims involved in the appeal is as follows:

46. A method of reducing blood pressure in a patient, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase, wherein said inhibitor is a compound or a pharmaceutically acceptable salt thereof having a structure of:



wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

48. A method of reducing hypertension in a patient, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase, wherein said inhibitor or a pharmaceutically acceptable salt thereof is a compound having a structure of:



wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

10. EVIDENCE APPENDIX

I. Evidence relied on by the Examiner with respect to the appealed grounds of rejection:

A. Blum, *et al.*, U.S. Patent No. 5,962,455

II. Evidence relied on by Appellants, and statement of where in the record that evidence was entered by the Examiner:

A. First Declaration under 37 C.F.R. § 1.132 of Dr. Bruce Hammock

Submitted with June 13, 2006 Amendment. Considered by the Examiner in the Non-Final Office Action dated August 23, 2006 and in the Final Office Action dated September 17, 2008.

B. Second Declaration under 37 C.F.R. § 1.132 of Dr. Bruce Hammock

Submitted with February 23, 2007 Amendment. Considered by the Examiner in Final Action dated May 11, 2007 and in Final Office Action dated September 17, 2008.

C. BLAST alignment between polypeptide sequence of human soluble epoxide hydrolase (sEH; GenBank accession number AAG14968) and polypeptide sequence of human neuropeptide Y1 receptor (NPY1R; GenBank accession number AAS55647)

Submitted with June 2, 2008 Amendment. Considered by the Examiner in the Final Office Action dated September 17, 2008.

D. BLAST alignment between human neuropeptide Y1 receptor (NPY1R; GenBank accession number AAS55647) and GenBank database.

Submitted with June 2, 2008 Amendment. Considered by the Examiner in the Final Office Action dated September 17, 2008.

E. BLAST alignment between human soluble epoxide hydrolase (sEH; GenBank accession number AAG14968) and GenBank database.

Submitted with June 2, 2008 Amendment. Considered by the Examiner in the Final Office Action dated September 17, 2008.

11. RELATED PROCEEDINGS APPENDIX

NONE.